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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/015,399 01/29/98 HINKKANEN

A 2328-111

EXAMINER

HM22/0811

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WASHINGTON DC 20004

VANDER VEGT, F

ART UNIT

PAPER NUMBER

1644

DATE MAILED:

08/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/015,399

Applicant(s)
Hinkkanen

Examiner
F. Pierre VanderVegt

Group Art Unit
1644



☒ Responsive to communication(s) filed on Jul 28, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-10 and 17-20 ~~is/are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-10 and 17-20 ~~is/are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-10 and 17-20 are currently pending in this application.

1. The Examiner in charge of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner F. Pierre VanderVegt of Group Art Unit 1644.

Continued Prosecution Application

2. The request filed on July 28, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/015,399 is acceptable and a CPA has been established. An action on the CPA follows.

3. In view of the CPA request filed July 28, 2000 without amendment to the claims, the following rejections are maintained. In the interest of completeness of the present record, the original grounds of rejection as well as the prior Examiner's responses to Applicant's arguments filed December 16, 1999 and May 25, 2000 are reiterated with each ground of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-5, 7-10 and 17 stand rejected under 35 U.S.C. 103(a) as obvious over US 5,547,669 to Rogers et al (issued August 20, 1996 filed December. 13, 1991) in view of Hummel et al (J. Autoimmunity 9:427, 1996), Verge et al (J. Autoimmunity 9:379, 1996), Rabin et al US 5,200,318 (issued April 6, 1993, fled May 13, 1992), Berg et al (Clinical Chemistry 43:2358, 1997), Berg et al (J. Immunological Methods 164:221, 1993) and Wiest-Ladenburger et al (Diabetes 46:565, 1997), all of record.

Claims 1-4 are drawn to fusion comprising epitopes of IA2, GAD65 and PPINS (preproinsulin). The elected species encompass a fusion protein comprising full length IA2, GAD65 and PPINS since the claims recite the term "comprises." Claims 5 is drawn to said fusion protein with a linker peptide provided with an affinity binding pair such as biotin-streptavidin. Claims 7-10 and 17 are drawn to DNA encoding the fusion protein and vectors comprising the DNA. Rogers et al teach fusion proteins comprising epitopes of at least two proteins and the use of such proteins to assay for T cell reactivity or antibodies to the epitopes comprising the fusion proteins. Rogers et al further teach that the epitopes may be derived from autoantigens (see abstract, column 6, lines 1-31, column 10, lines 31-60, column 13, lines 3-30, in particular). Rogers et al also teach that the fusion protein can comprise epitopes of autoantigens of diabetes and that such autoantigens include insulin, GAD, PM-1 and carboxypeptidase (see column 12, lines 12, lines 24-30, in particular). Rogers et al also teach that the epitopes can be linked together by linkers comprising amino acid sequence. Rogers et al disclose that the peptide linkers can comprise protease sensitive sites such as KK (Lys-Lys) or RR (Arg-Arg), thus disclosing fusion proteins comprising two or more epitopes linked by linker comprising lysine and arginine residues as is claimed in claim 4 of the instant specification (see column 15, lines 55-67, in particular). Rogers et al further teach that the fusion protein can be produced recombinantly or synthetically (see column 7, lines 61-67, in particular). Rogers et al disclose that the fusion protein can be made recombinantly by making cDNA encoding the fusion protein, vectors comprising said cDNA and expressing the vector in E. coli host cell (see column 19, lines 1-30, in particular). Rogers et al also teach that the fusion protein which is provided with (comprises) a member of an affinity binding pair, histidine. (see column 19, lines 30-45, in particular). Rogers et

al teach that histidine residues allow purification of the fusion protein by binding the protein to solid phase comprising nickel (see column 19, lines 30-45, in particular). Thus a fusion protein comprising a histidine sequence is a fusion protein provided with a member of an affinity binding pair as is claimed in claim 5.

5 Rogers et al does not exemplify a fusion product having an epitope of IA2, GAD and preproinsulin comprising the amino acid 771-979 of IA2, amino acid 102-585 of GAD and amino acids 1-110 of PPINS. The use of the term "comprising" in the claim language opens up the claims to read upon a fusion protein comprising the recited sequences but containing additional residues of the native protein or fusion proteins comprising intact IA2, GAD and PPINS.

10 The prior art teaches that patients with immune reactivity (serum antibody and/or T cell response) to IA2, GAD and preproinsulin are at risk for development of diabetes and that patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes.

15 Hummel et al teach that of newly diagnosed diabetes patients all showed reactivity to at least one recombinant islet cells antigen selected from insulin, GAD 65, and IA2 and that humoral and cellular immune reactivity to multiple islet cell antigens are present in patients with newly diagnosed type 1 diabetes and in high risk relatives (see abstract, in particular). Hummel et al teach that antibodies and cell mediated immune responses to IA2 are risk factors for the development of diabetes (see Figure 1 and 2 and page 428-429, in particular). Hummel et al teach that assaying for the presence of immune response to more than one autoantigen may become of increasing value in the diagnosis of preclinical type diabetes.

20 Verge et al teach that among first degree relatives of diabetes the five year risk of diabetes was 0% if antibodies to IAA, GAD, ICA512bcd are not detected, 15% if only one was positive, 44% if two were detected and 100% if all three were detected. Verge et al teach that 76% of new onset patients are positive for two or more autoantibodies and 98% were positive for one or more and 0% of control tested positive for more than one autoantibody. Verge et al also teach that with new onset insulin-dependent diabetes, the absence of any of these autoantibodies

justifies the consideration of non-autoimmune forms of diabetes in the differential diagnosis (see abstract, Figure 1, Figure 3, and page 382, in particular).

Rabin et al teach a method of diagnosing insulin dependent diabetes with an immunoassay which utilizes an immunoreagent comprising epitopes of GAD and ICA512 and ICA 12 (see abstract and claims 1-21, in particular). Rabin et al teach an immunoreagent that is a polymer backbone to which are attached multiples of one or more antigens and assays to determine reactivity of serum with immunoreagent (see column 7, lines 1-11 and column 7, line 24 through column 9, line 11, in particular). Rabin et al also teach assays in which the specificity of the serum (IE reactivity to one of the antigen attached to the backbone) can be determined (see column 8, line 57 through column 9, line 9, in particular).

Borg et al teach that assaying for antibodies to GAD and IA2 is useful in the diagnosis of diabetes and is an effective alternative to ICA assay. Borg et al teach that the of ICA positive patient only 5% of patients lacked both IA2 antibody and anti-GAD antibody and 52% of the patients had both anti-IA2 and anti-GAD antibodies, 24% had only anti- IA2 antibody and 18% had only anti- GAD antibody (see page 2360, in particular). Borg et al teach that by assaying for both IA2 and GAD antibody 95% of the ICA positive diabetes could be identified, but that 5% ICA patients have antibodies to other antigens. Borg et al also teach that in order to clarify the pathogenesis of IDDM determination of both antibodies to IA2 and GAD seem necessary.

Berg et al teach that sera from patients with recent-onset diabetes, 14% of the patients sera contain insulin autoantibodies which strongly recognized recombinant preproinsulin. Berg et al also teach that anti-GAD antibodies serves as the most relevant serological marker for ongoing β cell destruction and that generation of insulin autoantibodies alone confers relatively little risk for IDDM development (see abstract and page 22). Berg et al teach cDNA encoding preproinsulin and vectors and E. coli cells comprising said cDNA. The recombinant preproinsulin peptide comprises a histidine hexapeptide and GST (see page 229, in particular). Berg et al teach that the GST moiety introduces an enterokinase site and histidine hexapeptide permits single step purification by affinity chromatography using metal chelating Sepharose charged to NI ions. (see page 229, in particular). Berg et al teach that the use of preproinsulin to assay for autoantibodies

in patients permits the detection of antibodies directed against the C-peptide or signal peptide. Berg et al further teach that 11.6% of ICA positive sera were positive for anti-preproinsulin antibodies but that none of ICA positive serum were positive for anti-insulin antibodies (see page 229 and 230, in particular).

5 Wiest-Ladenburger et al teach that in most individuals developing IDDM, cytoplasmic islet cells antibodies (ICAs) circulate before and at the onset of the disease. Wiest-Ladenburger et al also teach ICA are the classical serological markers for diagnosis and prediction of IDDM, but high technical demands have limited the widespread use of histochemical ICA test. Wiest-Ladenburger also teaches that antibodies to IA2 and GAD65 represent major subfraction of ICA.
10 Wiest-Ladenburger et al also teach that ICAs also react with carboxypeptidase H, ICA69, proinsulin or insulin. Wiest-Ladenburger et al further teach that amino acid 603-979 of IA2 comprise epitopes recognized by ICAs. Wiest-Ladenburger et al also teach that a one-step assay for autoantibodies to IDDM autoantigens reduces costs and effort by more than 40% compared with separate testing, allowing an efficient large-scale screening of sera (see abstract and page 565
15 in particular).

 Thus the prior art teaches that patients with immune responses (antibodies and/or T cell reactivity) to GAD, IA2 and preproinsulin are at risk for the development of diabetes and that measuring antibodies to GAD, IA2 and preproinsulin is useful in the diagnosis of diabetes. The prior art teaches that that patients that have antibodies to more than one of these antigens are at
20 increased risk for the development of diabetes and the advantages of testing for reactivity to more than one IDDM autoantibody.

 Therefore one with ordinary skill in the art at the time of the invention would have been motivated to make a fusion protein such as the one taught by Rogers et al in which the autoantigens in the fusion protein comprise IA2, GAD and preproinsulin with the expectation that
25 patients could be screened for immune responses to the fusion protein to identify patients at risk for development of diabetes as is taught by Rabin et al or Wiest-Ladenburger et al since the prior art teaches that detection of immune responses to IA2, GAD and preproinsulin antibodies are useful in the diagnosis of diabetes and the identification of patients at risk for diabetes. One

would have been motivated to use such a fusion protein comprising the autoantigens in place of the immunoreagents taught by Rabin et al for ease of manufacture and consistency of the immunoreagent. One with ordinary skill in the art would have been motivated to combine the antigens into one immunoreagent (fusion protein) since the prior art teaches patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes and that one-step assays that simultaneously measure antibodies to more than one IDDM autoantigen allow for efficient and cost effective screening of sera. Fusion proteins comprising the linkers taught by Rogers et al meet the claim limitation of claim 4. Fusion protein comprising histidine hexapeptide linked to the linkers taught by Rogers et al meet the claim limitations of claim 5 since histidine is a member of an affinity binding pair and the art teaches that fusion proteins which comprise the histidine hexapeptide can be readily purified in a one-step purification protocol by binding the protein onto a Ni-Sepharose column. One with ordinary skill in the art would have been motivated to provide the fusion protein with a binding partner such as histidine to aid in the purification of the fusion protein as taught by Rogers et al and Berg et al or for use in immunoassays taught by Rabin et al. The use of the term "comprising" in the claim language opens up the fusion protein to read upon fusion proteins that comprise the intact IA2 or GAD amino acid sequence. One with ordinary skill in the art would have been motivated to make the fusion protein recombinantly by making a cDNA encoding the fusion protein, a vector expressing the DNA and expressing the vector in E. coli using the methods taught in the prior art to make fusion proteins with the expectation that the fusion protein encoded by the cDNA could be used in assays to screen for immune responses to the autoantigens comprising the fusion protein.

--Applicant's arguments filed December 16, 1999, Paper #9, have been fully considered but are not persuasive. Applicant's response that none of the prior art references teaches a fusion protein comprising preproinsulin is not persuasive. The prior art cited clearly teach that detection of immune responses to preproinsulin occurs in 14% of recent onset diabetics and indicates that measuring anti-preproinsulin antibodies is useful in diagnosing diabetics and that the presence of anti-preproinsulin antibody is a risk factor for diabetes. The prior art also teaches that anti-GAD and IA2 antibodies are risk factors for diabetes. The prior art also teaches the advantages of a

one-step assay for autoantibodies to IDDM autoantigens, IE reduction of costs and effort compared with separate testing. Thus the prior art teaches that patients with immune responses (antibodies and/or T cell reactivity) to GAD, IA2 and preproinsulin are at risk for the development of diabetes and that measuring antibodies to GAD, IA2 and preproinsulin is useful in the diagnosis of diabetes. The art teaches that that patients that have antibodies to more than one of these antigens are at increased risk for the development of diabetes and the advantages of testing for reactivity to more than one IDDM autoantibody. Applicant's response that the claimed fusion protein is a large protein (800 amino acid residues) and that it is unpredictable that proteins of this size will fold correctly to display the relevant epitopes. However, however there is no evidence of record to indicate the state of the art at the time the invention was made teaches that making fusion proteins comprising more than one epitope (i.e., relatively large fragments of a protein) is unpredictable. Rogers et al teach that fragments of antigens can be joined by linkers. Absent data to the contrary, one with ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success. Applicant urges that Rogers et al teach a preferred length of protein that is much less than the length of the instantly claimed fusion protein and urges that Rogers et al teaches away from the claimed invention. However, as stated supra, the state of the art at the time of the invention indicates that fusion proteins comprising relative large fragments of proteins can be made recombinantly. Rogers et al each that fusion peptides comprises at least 15%, more preferably at least 30%, 50 or up to 100% of the T cell epitopes of a protein (see column 7, lines 10-15, in particular). Rogers et al teach that the fusion proteins can comprise as many amino acid residues as desired. Rogers et al does teach that fusion proteins comprising relatively large fragments of peptides may retain an undesirable property, IE ability to bind to immunoglobulin. However, in the instant case, the ability to bind immunoglobulins is a desirable characteristic since the motivation to make the fusion protein is to use it to screen patient samples for antibodies to the protein. Applicant also urges that the protein may be limited to specific portions of IA2 or GAD65 since claim 3 recites particular amino acids sequences of these antigens. However, the claims are not limited to fusion proteins in which the epitope consists of amino acid 771-979 of SEQ ID NO:5 or 102-585 of SEQ ID NO:6. The use of the

term "comprising" in the claim language opens up the fusion protein to read upon fusion proteins that comprise the intact IA2 or GAD amino acid sequence.

--Applicant's arguments and the declaration of Ari Hinkkanen filed May 25, 2000 have been fully considered but are insufficient to overcome the rejections under 35 USC 103(a) set forth in the Office Action mailed February 28, 2000. The claims are under examination as they read upon the elected species of invention which is a fusion protein comprising epitope 771-979 of IA2, amino acid residues 102-585 of GAD, and 1-110 of PPINS and cDNA encoding such a fusion protein. PPINS is pre pro insulin. Thus the invention under examination is a fusion protein comprising epitopes of IA2, GAD and preproinsulin. The declaration filed May 25, 2000 does not provide evidence that the inventor was in possession of the invention as early as August 22, 1996 because the evidence relied upon as Exhibit 3 is not a certified English translation of Exhibit 1. If a certified English translation of Exhibit 1 is filed, it would be insufficient to overcome the rejections under 35 USC 103(a) because Exhibit 3 does not specifically disclose a fusion protein which comprises residues 1-110 of preproinsulin. The declaration discloses a fusion protein comprising GAD65/ICA512/Glioma 38kd, however, such evidence does establish that the inventor was in possession of the invention under examination. Applicant's argument that it was not known if a protein comprising fragments of more than one antigen could fold correctly to form a three dimensional structure with epitopes exposed is not persuasive. Fusion proteins from comprising fragments of more than one antigen or protein are well known in the art as evidenced by Rogers et al. Additionally the claims do not recite a limitation wherein the fusion protein must retain the three dimensional structure of the intact protein from which the fragments comprising the fusion protein are derived.

5. Claims 1-10 and 17-18 stand rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,547,669 to Rogers et al in view of Hummel et al, Verge et al, U.S. Patent No. 5,200,318 to Rabin et al, Borg et al, Berg et al, Wiest-Ladenburger et al and WO 94/07464 (issued March 16, 1994), all of record.

Rogers et al, Hummel et al, Verge et al, Rabin et al, Borg et al, Berg et al and Wiest-Ladenburger et al have been discussed supra. The invention claimed in claim 6 differs from the prior art in that the fusion protein comprises biotin or streptavidin. Here biotin is a label. However, WO 94/07464 teaches GAD labeled with biotin and the use of the biotin labeled GAD in immunoassays to detect antibodies to GAD. WO 94/07464 also teaches that autoantibodies to β -islet cell GAD may be extracted from patients serum, by binding to GAD and the complex to an insoluble or solid support. (See page 15, line 8 through page 16, line 20. Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a fusion protein comprising IA2, GAD and preproinsulin for the reasons discussed supra in which biotin is the binding member with the expectation that the biotin labeled fusion protein could be used to in immunoassays to screen sera for antibodies to IA2, GAD and preproinsulin.

6. Claims 19-20 stand rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5,547,669 to Rogers et al in view of Hummel et al, Verge et al, U.S. Patent No. 5,200,318 to Rabin et al, Borg et al, Berg et al, Wiest-Ladenburger et al and WO 94/07464 as applied to claims 1-10 and 17-18 above further in view of either U.S. Patent No. 5,316,909 to Xu et al (issued May 31, 1994, filed March 13, 1992) or U.S. Patent No. 5,637,509 to Hemmila et al (issued June 10, 1997, priority to December. 12, 1990), all of record.

Rogers et al, Hummel et al, Verge et al, Rabin et al, Borg et al, Berg et al, Wiest-Ladenburger et al and WO 94/07464 have been discussed supra. The invention claimed in claims 19 and 20 differs from the fusion protein discussed supra in that the label is radioactive or fluorescent (claim 19) or wherein the label is lanthanide (claim 20). However, the labeling of reactants in an immunoassay using a label such as a lanthanide is well known in the art as evidenced by Xu et al or Hemmila et al. Xu et al teach immunoassays in which one of the reactants is labeled with a radioisotope or fluorescent. Xu et al teach that lanthanides such as europium (Eu⁺), terbium (Tb³⁺), samarium, (Sm³⁺) or dysprosium (Du³⁺) can be used to fluorescently label immunoreactants in an immunoassay (see column 1, lines 5-30 and claims 1-2,

in particular). Hemmila et al teach labeling of analyte (antigen) with a lanthanide such as europium (EU3+) or terbium (TB3+) for use in an immunoassay (see claims 1-10, and column 7, lines 35-67, in particular).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a fusion protein comprising IA2, GAD and preproinsulin for the reasons discussed supra and to label it with a radioactive or fluorescent label such as a lanthanide with the expectation that such a fusion protein could be used in immunoassays to screen sera for antibodies to IA2, GAD and preproinsulin.

Conclusion

7. This is a CPA of applicant's earlier Application No. 09/015,399. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and odd-numbered Mondays (on year 2000 366-day calender) from 6:30 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.



F. Pierre VanderVegt, Ph.D.
Patent Examiner
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August 8, 2000



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